

I. THE INVENTION

The present invention relates, in part, to polynucleotides that are discovered using gene trap technology. The gene trap vectors used in the invention can integrate into intron sequences of cellular genes. The cellular genes in which the vector are inserted (the “trapped genes”) may be cloned easily since the vectors are designed such that fusion transcripts are formed with the trapped genes. The fusion transcripts comprise exon sequences of the trapped gene appended to a selectable marker that facilitates isolation by polymerase chain reaction-based protocols or by cDNA cloning. In some cases, integration disrupts the transcription of the trapped gene and results in a null mutation at the locus. In this application, the claimed invention relates to polynucleotides comprising the disclosed polynucleotide sequences of SEQ ID NOS:9-18 which are trapped genes obtained from human teratocarcinoma cells.

II. THE REJECTION UNDER 35 U.S.C. § 101 IS IN ERROR

Claims 3, and 10-14 are rejected by the Examiner under 35 U.S.C. § 101 as allegedly lacking patentable utility for the lack of a specific, substantial, and credible utility. Applicants respectfully traverse the rejection on the ground that Claims 3, and 10-14 are patentably useful and that the claimed invention has specific, substantial and credible utility.

Claims 3, and 10-14 recite polynucleotides comprising the disclosed polynucleotide sequences of SEQ ID NOS:9-18. Applicants submit that such polynucleotides have specific, substantial, and credible utilities as described in the specification.

According to the Examination Guidelines for the Utility Requirement (“Examination Guidelines”), if the applicant has asserted that the claimed invention is useful for any particular practical purpose (*i.e.*, it has a “specific and substantial utility”) and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 FR 1098 Jan. 5, 2001). A description of specific utility may be found in the Revised Interim Utility Guidelines Training Materials. Specific utility is:

“a utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a “gene probe” or “chromosome marker” would

not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.” (<http://www.uspto.gov/web/menu/utility>).

Unlike the example cited in the above definition where any fragment of genomic DNA can in theory be used as a probe or a chromosome marker, the polynucleotide sequences of SEQ ID NOS:9-18 have specific utility.

Gene trap vectors were introduced into human teratocarcinoma cells which result in the identification of the gene loci that comprise the sequences set forth in SEQ ID NOS: 9-18. After the gene trap vector had integrated into the human teratocarcinoma cell genome, fusion transcripts were expressed. Each fusion transcript comprises exons that are located either upstream or downstream from the integration site. These exons, which are portions of a genetic locus that was disrupted by a gene trap vector, were cloned and represented by the presently claimed polynucleotides.

The genetic loci which have been disrupted in the teratocarcinoma cells fall within a specific class of genes which are distinct from the broad general class of genes in the genome. Applicants point out that these genetic loci encode genetic functions, the full complement of which are not critically essential to the survival of teratocarcinoma cells. The teratocarcinoma cells, after transfection with the gene trap vectors, survived and propagated with only one non-disrupted allele of the genetic loci. Thus, these genetic loci and the products encoded by these loci are preselected by the transfection for possessing functions involved largely in later stages of cell differentiation and development.

Teratocarcinoma cells are the “stem cells” that occur in unusual germ cell tumors. Stem cells are defined by the ability both to produce identical daughter cells (self-renewal), and to produce progeny with more restricted fates (commitment and differentiation). This property of stem cells underpins growth and diversification during development and sustains homeostasis and repair processes throughout adult life. An understanding of molecular mechanisms which govern stem cell fate is therefore of fundamental significance in cell and developmental biology and the capabilities arising from such knowledge have major biomedical applications.

In many ways, teratocarcinoma cells resemble normal embryonic stem cells and represent a good model for molecular mechanisms of embryonic development and differentiation. These cells generate almost any kind of tissues such as teeth, hair, bone, muscle, and cartilage. When teratocarcinomas are injected into blastocysts, germ-line chimeras can be formed (Bradley et al., 1984, *Nature* 309:255-256). Applicants submit that genes that are critically essential to the survival of teratocarcinoma cells would not have been isolated and propagated by the gene trap methods of the invention, and would likely have been eliminated after the transfection with gene trap vectors. Thus, the sequences set forth in SEQ ID NOS: 9-18 represent a sample of genetic sequences that may play a role in late stages of cellular differentiation and development. Accordingly, the utility of these sequences are not general because not every gene in the genome, when mutated, necessarily provide the specific utility of the polynucleotides of the invention. Thus, Applicants submit that the claimed polynucleotides have specific utility.

Applicants submit that the utility of the claimed polynucleotides is substantial and credible because the claimed polynucleotides can be used as probes to facilitate the analysis of genetic loci that play a role during specific stages of embryonic development and cell differentiation.

As discussed earlier, since the genetic loci and the products encoded by these loci are preselected for the regulation in later stages of cell differentiation and development, the claimed polynucleotides can be used as probes in hybridization assays well known in the art to determine the activity at the genetic loci during development and differentiation of the teratocarcinomas (*See* for example, page 10, lines 29-33; page 28, lines 24-33; page 36, line 8 to page 37, line 19). Teratocarcinomas are totipotent which means that they may be differentiated into many different cell types (such as teeth, hair, bone, muscle and cartilage) along various pathways upon induction by certain signals. Each of these pathways may require expression of one or more genes that are disclosed in the specification as filed and represented by the presently claimed polynucleotides. Thus, the claimed polynucleotides can be used as probes, for example, in Northern blot analysis (page 36, line 8-11), or in situ hybridization (page 36, lines 11-15), for undifferentiated teratocarcinomas or differentiated teratocarcinomas of different lineages or at different stages of differentiation and development. The expression pattern of each of these genes can thus be correlated with

known events that occur in particular stages of development and cell differentiation. As such, the utility is substantial and credible in a real world context.

The polynucleotides of the invention can also be used for diagnostic gene expression and analysis, for cross species hybridization analysis, antisense inhibition, gene targeting, identifying exon splice junctions, gene therapy, gene delivery and chromosome mapping. *See* for example, page 10, lines 29-34.

Furthermore, the gene trapped sequences of the present invention overcome some of the limitations of conventional cDNA and expressed sequence tag libraries. In particular, the claimed polynucleotide sequences, were identified using gene trap vectors that do not rely solely on the degree of endogenous mRNA expression of a gene for identification of that gene. The gene trap vectors are able to identify poorly expressed genes.

The above described utilities are well known in the art and hence utilities of the present invention are credible. As stated in the Examination Guidelines for the Utility Requirement, credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure or any other evidence of record. (66 FR 1098, Jan. 5, 2001). Accordingly, not only do the polynucleotides of the present invention have specific utilities, their utilities are credible and practical.

In view of the foregoing, Applicants submit that the claimed invention has specific, substantial and credible utility.

III. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH SHOULD BE WITHDRAWN

Claims 3, and 10-14 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking utility. Applicants traverse this rejection on the ground that Claims 3, and 10-14 have significant patentable utility as discussed in Section II, above. Applicants submit that when an Applicant satisfactorily rebuts a rejection based on a lack of utility under 35 U.S.C. § 101, the corresponding rejection imposed under 35 U.S.C. § 112, first paragraph, should also be withdrawn. Thus, Applicants respectfully request that the rejection of Claims 3, and 10-14 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claims 3, and 10-14 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification. The Examiner states:

With the exception of the elected SEQ ID NOs, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, regardless of the complexity or simplicity of the method of isolation.

Applicants traverse this rejection on the ground that claims 3, and 10-14 indeed are fully supported by the specification and claims as originally filed.

35 U.S.C. § 112, first paragraph, requires that the specification contain a written description of the invention. An applicant must convey with reasonable clarity to those skilled in the art that the applicant was in possession of the invention. Vas-Cath v. Mahurkar, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). "The written description must communicate that which is needed to enable the skilled artisan to make and use the claimed invention." Kennecott Corp. v. Kyocera Int'l, Inc., 835 F.2d 1419, 1421, 5 U.S.P.Q.2d 1194, 1197 (Fed. Cir. 1987), cert. denied, 486 U.S. 1008 (1988).

Moreover, according to the Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1, "Written Description" Requirement (Federal Register v. 66, no. 4, pages 1099-1111, January 5, 2001, the "Guidelines"), the written description requirement may be satisfied by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Claims 3, and 10-14 recite isolated polynucleotides corresponding to one of SEQ ID NOS:9-18. The isolated polynucleotides are fully described by *structure* or by *physical properties*, or both, sufficient to distinguish the claimed isolated polynucleotides from other materials. For instance, Claim 10 recites isolated polynucleotide that comprises a contiguous stretch of at least about 30 nucleotides of at least one of SEQ ID NOS:10, 11, 15, 16. As the exact structure of SEQ ID NOS:10, 11, 15, and 16 are provided in the specification, although there are numerous polynucleotides that falls within this description, one person of skilled in the art can make the polynucleotide as described in claim 3. Likewise, Claim 14 describes a genus of polynucleotides by a property (*i.e.*, hybridizable under defined conditions to known sequences) that readily distinguishes the claimed

polynucleotides from other materials. One of skill in the art can readily isolate the claimed polynucleotides of Claim 14 and distinguish it from other polynucleotides by performing a hybridization as recited in the claim.

Applicants respectfully point out that the chemical structure of the claimed genus of nucleic acid molecules are described and well known in the art (e.g., DNA, RNA) and that the variation of nucleotide sequence within the claimed genus is also well defined by the functional characteristics of specifically binding under defined hybridizing conditions to nucleic acid molecules of known sequences. See footnote 42 of the Guidelines wherein it is stated that examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight, and length, and also detailed restriction enzyme maps, antibody cross-reactivity, unique cleavage by particular enzymes. One of skill in the art would recognize from the combination of identifying structural and functional characteristics disclosed in the specification that Applicants have possession of the claimed genus of nucleic acid molecules. In fact, the skilled person can readily recognize and determine whether a nucleic acid molecule falls within the pending claims by either comparing the sequence of the molecule with the sequences provided in the application and/or performing a hybridization reaction under defined conditions with the nucleic acid molecule(s) described in the present application. As such, Applicants submit that adequate written description has been provided.

The Examiner alleges that only the elected SEQ ID Nos per se, but not the full breath of the claims meet the written description provision and that the species specifically disclosed are not representative of the genus because the genus is highly variant. Applicants submit that the specification discloses exemplary elements that may be included in the claimed polynucleotides, such as non-coding or regulatory regions (page 20, lines 22-32); vector sequences (page 23, lines 17 to page 25, line 32), other coding sequences as obtained by “primer extension” (page 9, lines 16-21). As such, the specification is replete with description of representative elements that may be included in the claimed polynucleotides. Applicants submit that the written description requirement for the claimed genus of molecules are met.

In view of the foregoing, Applicants respectfully request that the rejection of Claims 3, and 10-14 under 35 U.S.C. § 112, first paragraph, be withdrawn.

CONCLUSION

Applicants submit that Claims 3, and 10-14 satisfy all of the criteria for patentability and are in condition for allowance, or at a minimum, narrow the outstanding issues and place the claims in better condition for appeal. Accordingly, Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application.

Respectfully submitted,

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Enclosures